Aus der Pferdeklinik,
Abteilung für Veterinäranästhesiologie
der Vetsuisse-Fakultät Universität Zürich
Leitung: Prof. Dr. med. vet. Jörg Auer

Arbeit unter der Leitung von Assistenzprofessorin Dr. med. vet. M. Paula Larenza
New Bolton Center, University of Pennsylvania, Philadelphia, USA

Anaesthesia recovery quality and immediate postoperative analgesia after racemic ketamine or S-ketamine administration to male cats undergoing routine neutering surgery

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vorgelegt von
Camila Nicole Balmer
Tierärztin
von Wilderswil (BE)

genehmigt auf Antrag von
Prof. Dr. Dr. med. vet. Regula Bettschart-Wolfensberger, Referentin
Prof. Dr. med. vet. Hanspeter Nägeli, Korreferent

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1. ABSTRACT

Anaesthesia recovery and analgesia qualities were compared in 20 client-owned male cats anaesthetised with intramuscular (IM) medetomidine (0.03 mg/kg) and S-ketamine (S-Ket: 6 mg/kg; n=10) or racemic ketamine (RacKet: 10 mg/kg; n=10). After routine orchiectomy, animals received IM atipamezole (0.15 mg/kg). Heart rate (HR) and respiratory rate (RR) were evaluated pre- and postoperatively. One blinded observer evaluated analgesia using a visual analogue scale (VAS; 0mm = no pain, 100mm = worst possible pain) and, by means of four-point scales, sedation, unprovoked behaviour and behavioural reactions to external stimuli 30 and 60 min after atipamezole administration. Cats with a VAS ≥ 15mm received butorphanol. Times to sternal (STERNAL) and standing positions (STANDING) were recorded. After 60 min, cats received carprofen (4 mg/kg) subcutaneously.
Anaesthesia with S-Ket, at 60% of RacKet, provided significantly faster recoveries (STERNAL: S-Ket=11±3 min, RacKet=30±19 min; STANDING: S-Ket=22±6 min RacKet=44±21 min) and increased postoperative RRs. Cats allocated to RacKet had higher HRs postoperatively at 30 and 60 min while those allocated to S-Ket had higher HRs only at 30 min. At 60 min, undisturbed cats in S-Ket had a trend towards fewer behavioural changes. Cats in RacKet were more sedate at 30 min and responded with a lower intensity to external stimulation. Immediate postoperative analgesia was judged adequate for both drugs.

2. INTRODUCTION

The commercial veterinary anaesthetic agent ketamine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist composed of two optical isomers (S and R) in a racemic mixture (Kharasch and Labroo 1992). Racemic ketamine has been in clinical use for more than 30 years and is considered to be safe and effective for most anaesthetic procedures, either during field or hospital conditions, regardless of species and/or route of administration (Marntell et al. 2006). Ketamine does not exhibit the respiratory depression seen with most other general anaesthetics (White et al. 1982) and also possesses sympathomimetic properties which counteract the cardio-depressive properties of other drugs (Schwieger et al. 1991). Conversly, ketamine produces a dissociative anaesthetic stage characterized by catalepsy, catatonia, and amnesia. The principal disadvantage of the drug, however, is that the use is associated with undesirable psychomimetic effects after anaesthesia, so called “emergence reactions” (White et al. 1982).

Early human studies of ketamine isomers (White et al. 1980) appeared to demonstrate that the S-isomer of ketamine produced less psychic emergence reactions than either the R-isomer or the racemic mixture. Moreover, the S-enantiomer has proven advantageous reaching an identical plane of anaesthesia with half of the racemic dose (Doenicke et al. 1992b). S-ketamine is less of a myocardial depressant compared to racemic and R-ketamine, as Graf et al. (1995) reported after using the isolated perfused heart model.

S-ketamine has also been recommended to be used for attenuating the post-operative hyperanalgesia in humans, (Ilkjaer et al. 1996) since S-ketamine presents an analgesic effect that lasts four times longer than racemic ketamine (Adams et al. 1992; White et al. 1985) and is approximately twice as potent as the racemic mixture in inhibiting central summation of pain (Arendt-Nielsen et al. 1996).

In this way, the S-isomer of ketamine seems to offer clinical advantages by using equipotent doses, causing less collateral effects than the racemic ketamine. Recently, the racemic form of ketamine has been withdrawn by the manufacturer from the human medical market in some european countries and replaced with S-ketamine (White et al. 2006).

In past years, S-ketamine has been introduced in veterinary practice as well. The use of S-ketamine has been reported in dogs, cats, horses and laboratory animals (Larenza et al. 2007a; Larenza et al. 2007b; Stelter 2001; Tunkel 2001; Wohlrab 2001). S-ketamine administered at half of the racemic ketamine dose was found to provide a similar degree of analgesia to clinically healthy cats (Stelter 2001) undergoing elective spay. It has been also used in moderate anaesthetic-risk (ASA III) feline patients providing a significantly faster recovery period and better post-operative analgesia and emergence quality than the racemic mixture (Baumgartner et al. 2002). Similar recovery quality and immediate post-surgical analgesia was observed in a previous study in female cats undergoing routine ovariectomy (Larenza et al. 2004). In that study, anaesthesia was induced either with racemic ketamine (10 mg/kg) or S-ketamine (6 mg/kg) intravenously and then maintained with isoflurane in oxygen. It was not clear whether these results were related with the similar anaesthetic actions of the two compounds, or if potentially dissimilar results were masked by the inhaled agent isoflurane or by gender-specific drug effects. Indeed, S-ketamine elimination was similar either after single enantiomer administration or within the racemate in ponies anaesthetised with isoflurane at one minimal alveolar concentration (Nolan et al. 1996). S-ketamine was favoured when given alone, if the ponies were sedated with the alpha-2 adrenoceptor agonist xylazine (Larenza et al. 2007a). These results suggested that the coadministered drug might have a significant impact over the metabolism of ketamine enantiomers.

Based on these studies, it was postulated that the association of S-ketamine with an alpha-2 adrenoceptor agonist would have a positive effect on the elimination of this enantiomer that might come clinically apparent as faster recoveries from anaesthesia in cats.

3. BACKGROUND

3.1. Isomerism

In chemistry, isomers are molecules with the same chemical formula and often with the same kinds of bonds between atoms, but in which the atoms are arranged differently (analogous to a chemical anagram). That is to say, they have different structural formula. The asymmetry of molecules is also called “chirality” (Ariens 1986).

Many isomers share similar if not identical properties in most chemical contexts. However, when they interact with biological systems, their effects over cell membrane receptors might exert different effects because their three-dimensional configuration varies. If dissimilar isomers bind to biological receptors several potential interactions can occur: they might induce the same intracellular reactions but to a lower degree (less efficacious compounds or partial agonists), or might induce the opposed reactions (antagonists) or they might just exert no reaction at all (inactive compounds) (Ariens 1986).

The realization that, in many cases, the different licensed drugs are isomers with different activities, has led to a rich new vein of active compounds to be produced in order to minimize side effects of partial agonists, antagonists or toxic compounds. These new products have been nominated in the pharmaceutical business as “chiral switchers”. The chiral switchers have been en vogue in the past few years, and several have reached the market with improved activity and, importantly, extended patent life. A good example in anaesthesiology is the local anaesthetic bupivacaine, which has been used for many years, particularly as an epidural anaesthetic/analgesic agent. Chiroscience discovered that the “L-isomer “ was substantially less cardiotoxic than the “R-isomer”, and was granted a patent for it on the basis of its lesser side-effects (Won et al. 2006; Brosnan et al. 2006).

3.1.1. History

Isomerism was first detected in 1827, when Friedrich Woehler prepared cyanic acid and noted that although its elemental composition was identical to fulminic acid (prepared by Justus von Liebig the previous year), its properties were quite different.

This finding challenged the prevailing chemical understanding of the time, which held that chemical compounds could be different only when they had different elemental compositions. After additional discoveries, such as the one from Woehler's in 1828, who realised, that urea had the same atomic composition as the chemically distinct ammonium cyanate, Jöns Jakob Berzelius introduced the term “isomerism” to describe that phenomenon (Freund 1968). In 1849, Louis Pasteur separated tiny crystals of tartaric acid into their two mirror image forms. The individual molecules of each image forms are the left and the right optical stereoisomers (Mason 1984). Solutions containing both optical stereoisomers rotate the plane-polarized light in opposite directions. In 1874, the Dutch chemist Van’t Hoff and the French chemist Le Bel introduced the theory of a chemistry in space for the first time by means of the molecular structure (Mason 1984). Years after, the Nobel Prize winner, Emil Fischer, explained that such chiral substances react according to the "lock-and-key principle", whereby an isomer better fits (Fischer 1902). This theory was confirmed later with the 3-point connection model by Easson and Stedman. The more effective isomer (Eutomer) binds with three ligands, wheras the less effective (Distomer) binds only with two ligands (Graf and Martin 1998).

3.1.2. Classification

There are two main forms of isomerism: structural isomerism and stereoisomerism.

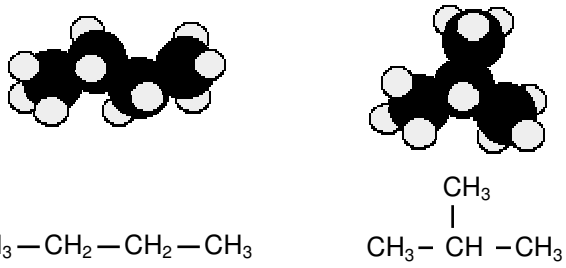
3.1.2.1. Structural isomerism

Structural isomerism is a form of isomerism in which molecules with the same molecular formula have atoms bonded together in different orders (Clark 2000). Structural Isomerism is further divided into the following three subgroups:

A. Chain isomerism:

These isomers arise because of the possibility of branching in carbon chains. For example, there are two isomers of butane, C_4H_{10} (Fig. 1). In one of them the carbon atoms lie in a "straight chain", whereas in the other the chain is branched.

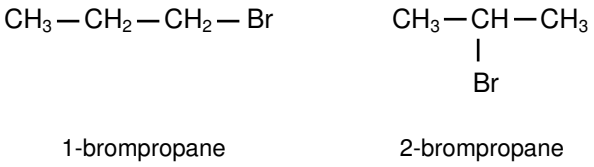
Figure 1: Chainisomerism: Two isomers of butane



B. Position isomerism:

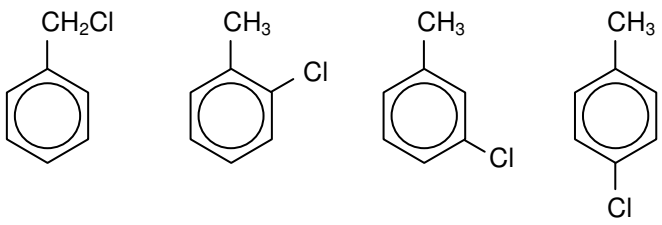
Positional isomers occur when a functional group changes position in the chain. The basic carbon skeleton remains unchanged, but important groups are moved around the skeleton. For example, there are two structural isomers within the molecular formula C3H7Br (Fig. 2). In one of them the bromine atom is on the end of the chain, whereas in the other it's attached in the middle.

Figure 2: Position isomerism of two structural isomers



Position isomers can be also obtained on benzene rings. Consider the molecular formula C_7H_8Cl (Fig. 3). There are four different isomers that can be made depending on the position of the chlorine atom. In one case it is attached to the side-group carbon atom, and then there are three other possible positions it could have around the ring-next to the CH_3 group, next-but-one to the CH_3 group, or opposite the CH_3 group.

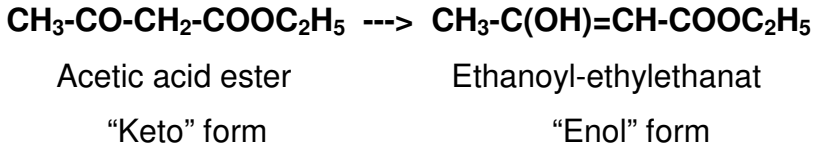
Figure 3: Position isomers on benzene rings



C. Tautomerism:

Tautomers are organic compounds that are interexchangeable by a chemical reaction called tautomerization. As most commonly encountered, this reaction results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond to an adjacent double bond (Katritzky et al. 1976). Tautometrism represents a special form of isomerism, in which an unstable structure isomer can convert to another isomer by change of the pH-value of the solution (Fig. 4).
For example:

Figure 4: Tautomerism



3.1.2.2. Stereoisomerism:

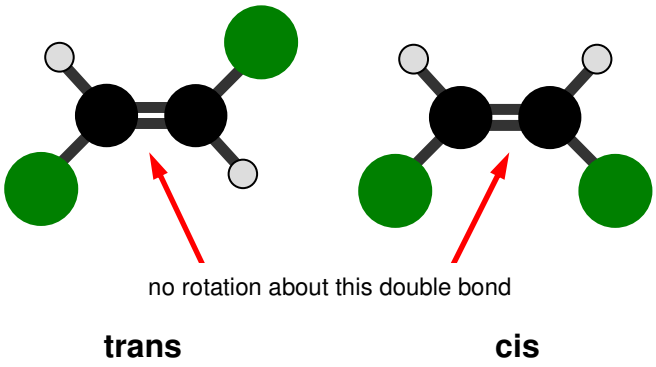
In stereoisomers the bond structure is the same, but the geometrical positioning of atoms and functional groups in space differs. This class includes enantiomers, where different isomers are mirror images of each other, and diastereomers in which the isomers are not mirror images. Stereoisomers can be divided into two sub-groups: geometrical and optical isomers.

A. Geometrical isomerism:

Geometric isomerism, also called cis-trans isomerism, is a form of stereoisomerism that describes the orientation of functional groups within the molecule. Such isomers typically contain double bonds which cannot rotate, but they can also arise from ring structures, where the rotation of bonds is greatly restricted. These isomers only occur in unsaturated compounds. Due to the double bond, the free rotation of the C-C-single bond is abolished and the substituents lie in a plane. There are two forms of geometric isomers: the cis and the trans versions.

When the substituent groups are oriented in the same direction the isomers are referred as cis and when the substituents are oriented in opposing directions the isomers are referred as trans (Fig. 5).

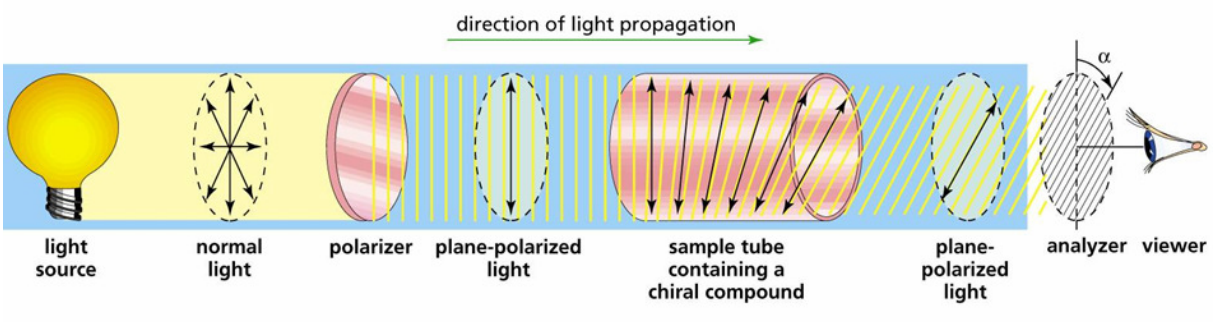
Figure 5: Geometrical isomerism



B. Optical isomerism:

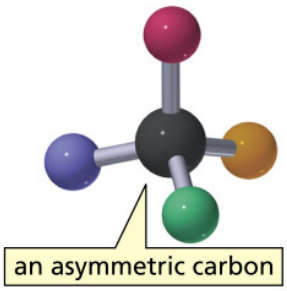
In optical isomerism the constituents have a different arrangement at the asymmetric carbon atom, which binds to four different ligands. Optical isomers are named as such because they can rotate plane-polarized light (Fig. 6).

Figure 6: Plane-polarized light



This property is a consequence of their asymmetrical C-atom which is optically active (Fig. 7).

Figure 7: Asymmetric C-atom

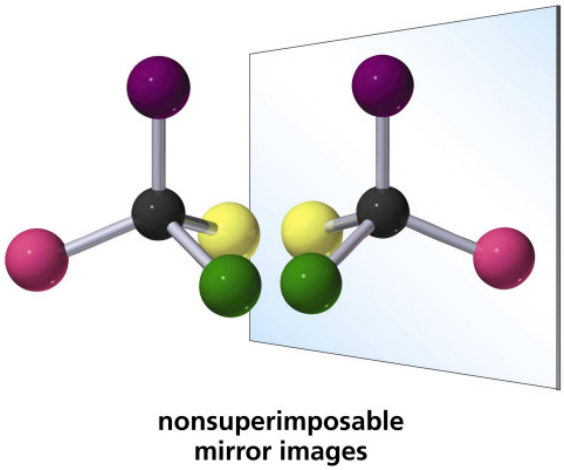


When one enantiomer rotates the plane of polarisation in a clockwise direction it is known as the **(+)** form or **dextrorotatory**. An example is the optical isomer of the amino acid alanine, which is known as (+)-alanine.

On the contrary, when an enantiomer rotates the plane of polarisation in an anti-clockwise direction it is known as the **(-)** form or **laevorotatory**. In the previous example of alanine the other enantiomer is known as (-)-alanine.

In addition, enantiomers have a particular spatial arrangement and are described as being non-superimposable mirror images of each other (Fig. 8).

Figure 8: Nonsuperimposable mirror images

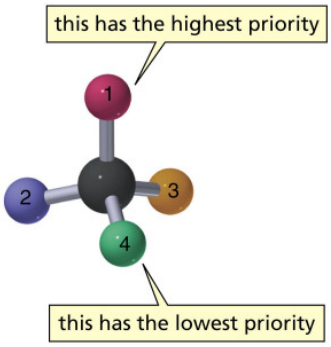


Racemic mixtures or racemates often occur as a 1:1 mixture of the two enantiomers (+ and -). As the amount of polarized light rotation caused by each of the two isomers is exactly the same but in opposite directions a racemate has no effect on plane-polarized light.

The expression "racemic" comes from the tartaric acid (acidum racemicum) on which that feature was first observed by Louis Pasteur (Mason 1984).

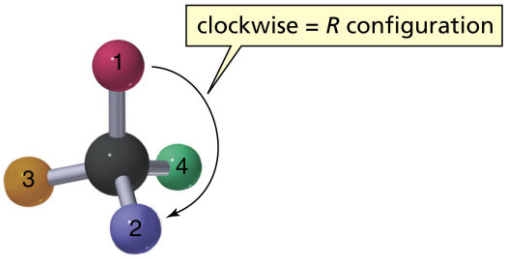
Independently of the direction of rotation, the optical enantiomers can be also named according to their isometric molecules. Cahn et al. (1956) instituted a set of rules which assigns priorities to the substituents attached to the asymmetric carbon (Fig. 9).

Figure 9: Priorities of substituents attached to the asymmetric carbon



The molecule is then viewed with the lowest priority group away from the viewer. If the direction of rotation from the highest to the lowest priority group is to the left (anticlockwise) the enantiomer can be described as “S” (sinister) and if the rotation is to right (clockwise), then the molecule is “R” (rectus) (Fig.10).

Figure 10: “R” configuration



In the past, R- and S-enantiomers were called as D- and L-compounds, respectively (Fischer 1902) .

3.2. Dissociative anaesthetics

Cyclohexanonderivates like phencyclidine, tiletamine and ketamine belong to the group of dissociative anaesthetics. Phencyclidine is no longer available to the practicing veterinarian because of its addictive potency. Tiletamine is only approved for use in combination with a benzodiazepine derivate called zolazepam, in a 1:1 drug combination. Ketamine is the most commonly used dissociative agent for animal anaesthesia (Mama et al. 2005).

Typical clinical indications of this group of anaesthetics are analgesia, unconsciousness and immobilization. Dissociative anaesthetics can exert exhilarating effects like catalepsy (Winters et al. 1988) with the patients keeping their eyes open and maintaining their swallowing and corneal reflexes and with different degrees of muscle rigidity. Spontaneous movements may occur, which are independent from painful stimuli (White et al. 1982).

Dissociative anaesthetics owe their name to their mechanism of action. Different studies showed that the neuronal signal transmission is suppressed in the reticular formation of the brain as a result of a functional and electro-physiological dissociation between thalamo-cortical an limbic system (Massopust et al. 1972).

3.3. Ketamine

3.3.1. History

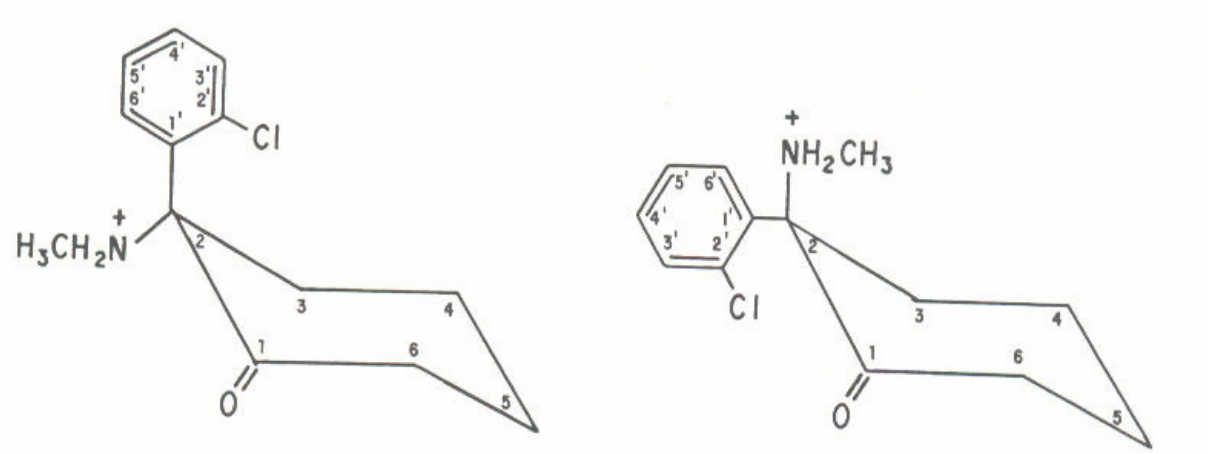
Ketamine, a derivate of phencyclidine, was developed in 1956 by Parke-Davis, the pharmaceutical company. Six years later, ketamine was synthesised by another american pharmaceutical company named Dupont. In 1965, this new anaesthetic was clinically tested for the first time in twenty volunteers (Domino et al. 1965) and was admitted into the american human medicine market. In 1970, ketamine was registered for cats. Since then, it was firmly established as intravenous anaesthetic in the veterinary field because of its big therapeutic window in almost all vertebrates.

3.3.2. Physicochemical characteristics

Ketamine hydrochloride is chemically marked as 2-(2-chlorophenyl)-2-methylamino-cyclohexanon and resembles phencyclidine and cyclohexamine. Ketamine has a molecular weight of 238 kd, is partially water soluble, and forms a white crystalline salt with a negative log of the acid ionization constant (pKa) of 7,5.

PH-value of watery solution of ketamine is 3,5. Therefore tissue irritation can occur after intramuscular injection (Booth 1988). Lipid solubility of ketamine is five to ten times higher than that of thiopental (Cohen and Trevor 1974).
A ketamine molecule contains a chiral center at the C2-position of the cyclohexane ring and therefore occurs as two resolvable optical isomers: S(+)- and R(-)-hydrochloride (Fig 11). The most widely used commercial preparation of ketamine is a racemic mixture although, recently, the S-enantiomer has been registered for cats in Switzerland.

Figure 11: Ketamine isomers:



S(+)-ketamine hydrochloride R(-)-ketamine hydrochloride

(Miller 2000)

3.3.3. Pharmacokinetics

Ketamine can be applied to cats, both intravenously and intramuscularly. Thanks to its high lipid solubility, ketamine penetrates the blood brain barrier fast and can develop its effect on the CNS only after a very short period of time (Cohen and Trevor 1974). In most species, the highest ketamine concentration in plasma after an intravenous application is achieved after one minute and around five minutes after an intramuscular application (Kaka and Hayton 1980; Kaka et al. 1979; Larenza et al. 2007a; Larenza et al. 2007b; Matthews et al. 1994; Pypendop and Ilkiw 2005; Waterman 1984; Wieber et al. 1975; Woods et al. 1999).

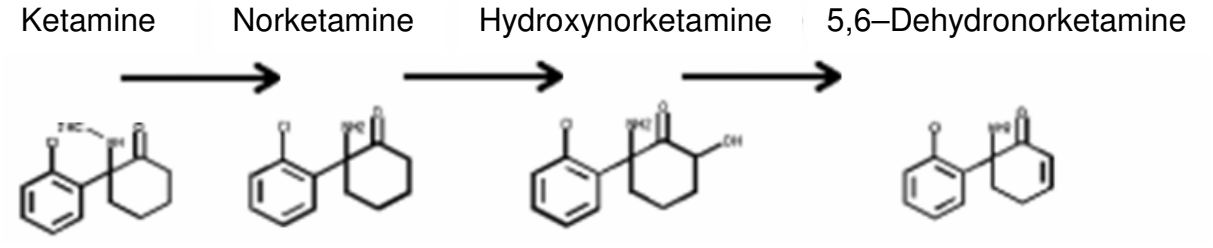
Ketamine is first distributed to tissues that are well supplied with blood. This initial distribution phase of the central compartment (plasma) to the peripheral compartment (tissue) happens with a half-life ($T_{1/2\alpha}$) of 7-11 minutes. Compared to the plasma, a 4-5 times higher concentration is reached in the brain within 30-90 seconds. Later, ketamine is redistributed from tissues that are well supplied with blood, to tissues suboptimally supplied with blood. This redistribution has been found responsible for termination of hypnotic and anaesthetic effects (Cohen and Trevor 1974). The elimination phase, which reflects both metabolic and excretory processes has a half-life ($T_{1/2\beta}$) of three hours in man (Clements and Nimmo 1981). Ketamine is not strongly bound to plasma proteins (around 50%) (Hijazi and Boulieu 2002; Kaka et al. 1979).

In cats, $T_{1/2\alpha}$ was found to be 2.7 minutes and $T_{1/2\beta}$ 78.66 minutes, with a volume of distribution of 1.5 l/kg (Hanna et al. 1988a). The plasma protein bond in cats is even lower than other species, with a bound fraction of only 37.54% (Hanna et al. 1988b).

Other medicaments or anaesthetics can influence pharmacokinetics of ketamine. Halothane for example prolongs spreading and redistribution of ketamine and impedes hepatic metabolism. Both effects prolong CNS effect of ketamine. Also diazepam, which can be used as a premedication to reduce muscle contractility caused by ketamine, prolongs $T_{1/2\alpha}$ of ketamine and therefore delays postoperative awakening.

In most species, the hepatic microsomal enzymes (PYE-450) methylate ketamine to metabolite-1 or norketamine, which only has 1/5-1/3 of the effect of the original compound. Norketamine is further hydroxylated to metabolite-2, hydroxynorketamine, which is conjugated in another step with water-soluble glucuronates and is finally eliminated with urine (Chang and Glazko 1974) (Fig. 12).

Figure 12: Methylation of ketamine to hydroxynorketamine



The cat represents an exception in such metabolic pathways since the second step of this cascade shows very low action (Hanna et al. 1988a). The biggest part of injected ketamine is eliminated unchanged by the kidneys and only small quantities are metabolised to norketamine in the liver.
Animals with hepatic deficiency might metabolise ketamine slower than healthy animals. Cats with kidney failure or lower urinary tract obstruction might have a longer post operative recovery, since ketamine and its metabolites cannot be eliminated fast enough (Short 1987).

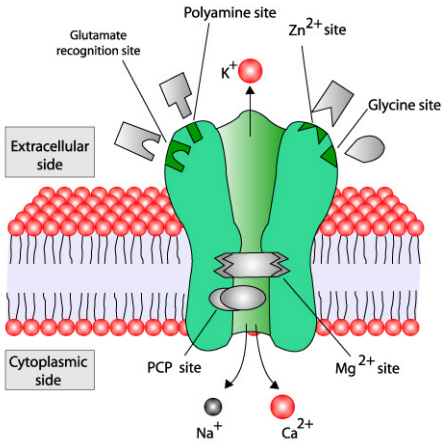
Pharmacokinetics of S(+) isoforms of ketamine and norketamine differ from the R-isoforms (White et al. 1985). Studies in liver microsomes explained this phenomenon after having noticed a stereo selectivity elimination of R- and S-ketamine (Kharasch and Labroo 1992). When S-ketamine is administered within the racemate, its elimination is inhibited by the R-enantiomer, resulting in higher clearance for S-ketamine when given alone (Ihmsen et al. 2001; Larenza et al. 2007a). This higher S-ketamine clearance was considered to be responsible for the faster recovery from anaesthesia in horses and humans (Ihmsen et al. 2001; Larenza et al. 2007a).

3.3.4. Molecular pharmacodynamics

The molecular pharmacodynamics of ketamine is complex, since it interacts with different binding sites like N-methyl d-aspartate (NMDA) and non-NMDA-glutamate-receptors, nicotinic- and muscarinic acetylcholine receptors, monoamine neurotransmitters and opioid receptors (Cai et al. 1997; Kress 1997; Yamakura et al. 1999; Petrovic et al. 2005; Foster and Kemp 2006; Kohr 2007; Maeng et al. 2007; Snyder et al. 2007). Additional interactions with voltage gated Na^{+}- and Ca^{2+}-channels were also described (Wong and Martin 1993). Despite the complexity ketamine mechanisms of action, the NMDA-receptor-antagonism effect is responsible for most of analgetic, amnestic, psychomimetic and neuroprotective effects of this agent (White et al. 1982).
NMDA-receptors occur in a high density primarly in the cortex, hippocampus, thalamus and striatum. In the spinal cord NMDA-receptor contributes to the diminution of polysynaptic conduction. NMDA-receptor is an ionotropic receptor, which is activated by glutamate (excitatory neurotransmitter) (Fig. 13).

The channel is generally continuous for Ca^{2+}- and partly also for Na^{+}- and K^{+}-ions. Glycine is an obligatory co-agonist and Mg^{2+} impedes the ion channel. NMDA-receptors are involved in the winding up phenomenon, central sensitisation responsible for hyperalgesia and pain memory, which plays a role in the emergence and maintenance of chronic pain (Woolf 1989). NMDA-receptor is the postsynaptic neural effect site for ketamine (Kohr 2007; Kohrs and Durieux 1998). Ketamine binds to the phencyclidine (PCP) site of the NMDA channel and thereby noncompetitively impedes glutamate to activate it. Thus, ion transport is reduced. The blockade is time, concentration, and frequency dependent (MacDonald et al. 1987).

Figure 13: NMDA receptor



S(+)-ketamine has 3-4 times stronger affinity for NMDA-receptors than R(-)-ketamine. That corresponds to the proportion of different analgesic and anaesthetic potency of the two isomers (White et al. 1980; White et al. 1985). However, R(-)-ketamine was found to cause stronger psychomimetic side effects than S(+)-ketamine. In overall ketamine-side-effects controversy, participation of other receptors like σ-opioid-receptors has been suspected (Kress 1997). Racemic ketamine and R(-)-ketamine showed as well significant activity over the κ-opioid receptors. Both, σ- and κ-opioid receptors have been associated with psychomimetic side effects produced by opioids (Finck and Ngai 1982). On the other hand, S(+)-ketamine interacts more with μ- than κ-opioid receptors, which has been associated with most of analgesic effects produced by opioids. However, analgesic effects that result from ketamine binding to opioids receptors seem to be minor (Kress 1997).

Ketamine also influences nicotinic and muscarinc acetylcholine receptors, by impeding NMDA-receptor-mediated distribution of acetylcholine (Kress 1997).
In addition, ketamine isomers showed differences after binding to adrenergic, dopaminergic and serotoninergic receptors (Lindefors et al. 1997; Ylitalo et al. 1976).
Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter found in the central nervous system. Whether ketamine interaction with GABA receptors has an impact over its overall pharmacodynamics remains to be determined. Although a significantly increased GABA-induced Cl^- flow was determined (Lin et al. 1992) after very high ketamine dosages, these results might be clinically irrelevant.
Both, R(-)-ketamine and S(+)-ketamine impede intraneural uptake of catecholamines and serotonine (Tso et al. 2004). In addition, S(+)-ketamine impedes extraneural uptake of catecholamines. Intraneural uptake of serotonine inhibition of R(-)-ketamine was stronger than that of S(+)-ketamine. When racemic ketamine or S(+)-ketamine are combined with midazolam, increases of adrenaline and noradrenaline can be minimized (Adams et al. 1981; Doenicke et al. 1992a).

3.3.5. Effects on the cardiovascular system

Cardiovascular activity of ketamine is accomplished by different effects, which indirectly cause a stimulation of the heart (Kohrs and Durieux 1998):

- sympathomimetic effects
- inhibition of neuronal uptake of catecholamines by sympathetic nerve endings
- direct vasodilatation
- inotropic effect on the myocardium

Heart rate and the arterial blood pressure increase as a result of the direct stimulation of the central nervous system, which causes an increase in cardiac output (Bettschart-Wolfensberger et al. 1996; Boscan et al. 2005).
Studies in humans showed that arterial blood pressure increased 25%, whereas heart rate increased 20% of the initial values. These increases were similar for either 2mg/kg reacemic ketamine or 1mg/kg S-ketamine given intravenously (Adams et al. 1992). Within two minutes after an intravenous administration of ketamine, blood plasma concentrations for adrenaline and noradrenaline increased. Fifteen minutes later these concentrations diminished again to baseline values (Baraka et al. 1973).

After application of 2 mg/kg racemic ketamine or 1mg/kg S-ketamine intravenously, the same level of catecholamines and cortisol were measured.
Although adrenaline release is lower after S-ketamine administration, it does not lead to significant differences in stimulatory effects over circulation (Doenicke et al. 1992a).
Direct effect of ketamine on the myocardium is controversial. Increased myocardial stimulation is associated with an increased work of heart and myocardial oxygen consumption. Coronary blood flow increases parallel with increased oxygen consumption, but might not match it (Sonntag et al. 1972) leading to potential myocardial ischemia. Cardiovascular stimulation after ketamine administration can be diminished by coadministered sedatives (Doenicke et al. 1992b; Mama et al. 2005). Racemic ketamine has negative inotropic effects (Smith et al. 1979). However, in in-vitro heart models with an intact autonomic nervous system, the centrally stimulating effects of ketamine prevailed over its myocardial depressing actions (Chodoff 1972). On the other hand, in isolated guinea pig hearts, a significantly less depressive effect was shown for S(+)-ketamine than for R(-)-ketamine (Graf et al. 1995).

3.3.6. Effects on the respiratory system

Ketamine differs from most other anaesthetics in that it does not depress ventilatory responses to hypoxia (Booth 1988). Dog's respiratory rate and minute volume decrease initially when anesthetised with ketamine, but both return to baseline values within 15 minutes (Haskins et al. 1986b; Haskins et al. 1986c). In cats, ketamine induces a transient decrease of PaO_2 in the presence of decreased or increased respiratory rate (Haskins et al. 1975). Ketamine also induces a dose dependent apnea. If ketamine is administered rapidly by intravenous injection it often causes the patient to stop breathing for a short time (up to one minute). An overdose normally leads to a severe respiratory depression (Kohrs and Durieux 1998). After a slow intravenous induction, breathing is well maintained and may even increase slightly. The airway is usually well maintained during ketamine anaesthesia and there is some preservation of pharyngeal and laryngeal reflexes in comparison with other intravenous agents. However, this cannot be guaranteed and normal airway care must be maintained to prevent obstruction or aspiration. Usually, cats can be endotracheally intubated after ketamine administration as an induction agent and after application of lidocaine onto the larynx.

Ketamine often causes increased salivation and secretation of respiratory tract mucus, (Bednarski 1996) however, administration of atropine to prevent them is controversial. Ketamine produces some bronchodilation making it a useful anaesthetic drug for patients with asthma. This property is mainly due activity of the R-enantiomer (Pabelick et al., 1997).

3.3.7. Effects on the central nervous system and awakening phase after ketamine anaesthesia

Ketamine produces dose-related unconsciousness and analgesia. The primary site of central nervous system (CNS) action of ketamine appears to be the thalamoneocortical projection system. The drug selectively depresses neuronal function in parts of cortex and thalamus, while simultaneously stimulating parts of limbic system, including hippocampus (Miyasaka and Domino 1968). Nociceptive cells of the reticular formation are inhibited and laminae I and V in feline dorsal spinal horn are activated (Ohtani et al. 1979). NMDA-receptor antagonism can cause an anticonvulsive feature at a low dosage of ketamine (Reder et al. 1980). Nevertheless, cases of epileptic cats are described, in which ketamine has triggered seizures (Evans et al. 1972). In the past, ketamine was thought to induce significant increases in cerebral blood flow (CBF), intracranial pressure (ICP) and cerebrospinal fluid (CSF) pressure as a result of cerebral vasodilatation and elevated systemic blood pressure (Evans et al. 1971). However, this concept has been recently revisted, and the direct effect of ketamine over ICP could not be demonstrated. It was thought that increases in ICP, CBF and CSF seen in former studies were mainly due to hypoventilation which leads to carbon dioxide accumulation and cerebral vasodilation (Himmelseher and Pfenninger 1998).

Hallucinatory behaviour, which may progress to delirium, may occur during emergence from ketamine anaesthesia. These effects occur because of the inhibition of the inferior cunniculus and medial nucleus geniculatum, which in turn leads to misinterpretation of the auditory and visual stimuli (White et al. 1982).

Different authors described such reactions in cats as typical behaviour after ketamine anaesthesia like ataxia, increased motor activity, hyperreflexia, increased sensibility when touching, fear of an invisible object up to aggressiveness during awakening phase (Wright 1982).

Recently, the following emergence reactions from ketamine anaesthesia in cats have been described (Eichenberger 2005).

Eyes: Mydriasis (prolonged dilatation of the pupil of the eye).
Head: Head on plane of body with moving it toward one side, from one side to the other, moving it up and down or combined movements.
Ataxia: - Minor ataxia (minor coordinated movements): crawling.
- Moderate ataxia: switching weight from one leg to the other.
- Severe ataxia: falling to one side, rolling over, circling.
Rigid muscular tone: In lateral recumbency legs are straight but not touching the floor. Often seen as stif hindlegs, pedalling or spontaneous leg movements. In sternal recumbency legs are not under the body.
Excitation: - Minor excitation: crawling, turns head, salivation.
- Moderate excitation: restless moaning, combined head movements licking the lips, exploring the cage.
- Severe excitation: unsolicited vocalizations, very restless, expiratory grunts, rolling over, climbing the cage, frequent tongue movements.
Bizzarre activity: crawling, switching weight from one leg to the other, falling to one side, rolling over, jumping, circling, walking backwards, intend to escape, general body tremors, frequent tongue movements and licking the lips.

Simultaneous administration of alpha-2 adrenoceptor agonists or benzodiazepines can reduce such undesirable reactions (Doenicke et al. 1992b; Haskins et al. 1986a; Haskins et al. 1986c; Haskins et al. 1975; Mama et al. 2005).
In humane medical studies, dream experiences appeared in a similar frequency but in different quality after S(+)-ketamine application in comparison with the racemate (Dundee and Wyant 1988; White et al. 1982). Excitation and disorientation as well as post-operative fear were rarer after S(+)-ketamine administration than after R(-)-ketamine administration. Unlike the racemate most patients would choose S(+)-ketamine for next anaesthesia. Another study showed a faster post -operative recovery after S(+)-ketamine anaesthesia.

Also the subjective evaluation turned out better after S(+)-ketamine administration. The incidence of dream like experiences was the same in the two groups (Doenicke et al. 1992a). Ponies receiving either racemic ketamine or S(+)-ketamine at half of the racemic dose recovered faster from anaesthesia when S-enantiomer was administered (Larenza et al. 2007a). These effect was associated with a faster elimination of S(+)-ketamine when administered alone than when administered as part of the racemate.

3.3.8. Analgesia

In humans, ketamine, administered at subanaesthetic doses, develops strong analgesic effects (Arendt-Nielsen et al. 1996; Himmelseher and Pfenninger 1998; Hirota and Lambert 1996; Lauretti et al. 1999; Lauretti et al. 2001; Oye et al. 1992; Schuttler 1992). S(+)-ketamine develops stronger analgesic effects than racemic ketamine or R(-)-ketamine (Pfenninger et al. 1994).

In cats the degree of analgesia produced by ketamine appears to be greater for somatic pain than for visceral pain (Haskins et al. 1975). In cats visceral analgesia induced by ketamine (4 mg/kg intravenously) is similar to that produced by butorphanole (0.1 mg/kg intravenously). There is no increase of the visceral analgesia if ketamine dose is elevated or ketamine is administered in combination with butorphanol (Sawyer et al. 1990).

Ketamine anaesthesia is normally suitable for short surgical interventions, particularly for surgery at the skeleton, extremities and integument. For such short interventions ketamine might even provide sufficient analgesic effects during the post-operative phase. For instance, both, S-ketamine (6 mg/kg IV) and racemic ketamine (10 mg/kg IV) showed good immediate postoperative analgesia in female cats undergoing ovariohysterectomy (Eichenberger 2005). However, ketamine alone does not suffice against visceral pain which emerges in long-lasting operations in the thorax or abdomen (Himmelseher and Pfenninger 1998).

Several mechanisms are involved in the analgetic effect of ketamine (Arendt-Nielsen et al. 1996; Cai et al. 1997; Finck and Ngai 1982):

- Blockade of the spinoreticular tracts
- Inhibition of the reticular formation
- Rejection of the activity of the Lamina I and V
- Interaction with opioid-receptors of the central nervous system
- NMDA-receptor antagonism

3.3.9. Anaesthesia potency of racemic or S(+)-ketamine

Experiments with rats and mice showed that S(+)-ketamine was three times more analgesic and had 1,5 times more hypnotic effects than the R(-)-ketamine (White et al. 1985). Further, data of the same study gave hints that S(+)-ketamine seems to be twice as potent as the racemate.

In other experiments with mice, the therapeutical index was determined and was 2,5 times bigger for S(+)-ketamine than for R(-)-ketamine or the racemate (Ryder et al. 1978). Since the S(+)-isomer is stronger, half dose of the racemate suffices for anaesthesia (Schuttler 1992). Consequently, the amount of necessary drug decreases considerably for the patient, and thus its side effects as well. In studies with human beings and ponies, shorter post operative recoveries were detected after S(+)-ketamine in comparison to the racemate (Adams et al. 1992; Doenicke et al. 1992b; Larenza et al. 2007a).

Classic side effects of ketamine anaesthesia like amnesia, less concentration ability, unpleasant dreams, nausea and vomitus were observed in humans after anaesthesia with ketamine with similar frequency after administration of both S(+)-ketamine or the racemate (White et al. 1980). Nevertheless, most patients felt better after the administration of S(+)-ketamine and would prefer it compared with the racemate (Doenicke et al. 1992b). The reduced movements, less disorientation and less fear were predominantly reasons for feeling better after the administration of S(+)-ketamine (White et al. 1980).

4. MATERIALS AND METHODS

4.1. Study design and test animals

The experimental trial was designed as a blinded randomised prospective study. A total of 20 client-owned male cats with a low anaesthetic risk (ASA I-II) (Hosgood and Scholl 2002) entered this study. They were brought to the anaesthesia section of the Vetsuisse-Faculty, University of Berne by their respective owners the day of the trial. Once the cats arrived at the faculty facilities, they were housed in plastic kennels at room temperature and in a quiet environment until sedation was administered. Food was withheld twelve hours before surgery to avoid the hazards of aspiration. Free access to water was granted until one hour prior to the surgery and after complete recovery from anaesthesia. Immediately after surgery they were kept in a transparent infant incubator (Isolette Model C200, Ing. Nufer AG, Bern) for 60 minutes, at controlled temperature (25-26°C), and breathing room air. The animals were allocated into two groups (S-Ket, n=10; RacKet, n=10) making use of the envelope system. Blinding was ensured by preparing two separated vials (A and B) containing either S-ketamine 60 mg/mL (Keta-S ad us.vet., Dr. E. Graeub AG, Bern, Switzerland) or racemic ketamine 100 mg/mL (Ketasol-100, Dr. E. Graeub AG, Bern, Switzerland), which allowed for an equivalent volume of each solution to be used in order to reach the appropriate dosage for each cat (0.1 mL/kg). The anaesthetist remained unaware of the treatment identity.

4.2. Pre-admission examination and inclusion-exclusion criteria

The pre-admission examination included the data of the patient (patient's name, owner's surname, breed, age, sex), group allocation (S-Ket or RacKet), anaesthetic risk of the American Society of Anesthesiologists (ASA) classification (ASA I-II: low anaesthetic risk; ASA III: moderate anaesthetic risk; ASA IV-V high anaesthetic risk anamnesis, the physical examination: body condition (weight, hydration status, temperature), cardiovascular and respiratory system (respiratory frequency, cardiac frequency, mucous membrane colour, capillary refill time, pulse character, thoracic auscultation), other systems evaluation and the concomitant drugs given (Hosgood and Scholl 2002).

The inclusion criteria were: ASA I, II (suitable to receive general anaesthesia) non-sterilised male cooperative cat. Animals were excluded when they were ASA III-V (non-suitable to receive general anaesthesia), female or male but already sterilised and/or non-cooperative.

4.3. Anaesthesia and surgery

Medetomidine (Domitor, Orion Corporation, Espoo, Finland) at a dose of 30 µg/kg was administered intramuscularly for pre-anaesthetic sedation. Approximately five minutes later, racemic or S-ketamine (solutions A or B) were administered as single intramuscular injection at a dose-volume of 0.1 mL/kg (10 mg/kg for racemic ketamine; 6 mg/kg for S-ketamine). When the cats lost their righting reflex and showed no reaction to pin-prick stimulation of the skin, they were placed in their dorsal recumbency. Throughout anaesthesia, a transparent plastic face mask was used to provide oxygen enriched air. The hemoglobin oxygen saturation (SpO_2) was determined with a pulse oximeter infra-red probe placed on the tongue. Hypoxaemia was defined as SpO_2 below 90%. A lead II electrocardiogram was displayed and the heart rate (HR) was calculated in beats/minute and bradycardia was defined as HR < 80. Rectal temperature in °C was recorded at the end of the surgery and hypothermia was defined as rectal temperature < 37°C. A portable anaesthesia monitor (Datex S-5 portable anaesthesia monitor, Datex-Ohmeda, Helsinki, Finland) continuously displayed the aforementioned data during the anaesthetic episode. Respiratory rate (RR) was calculated by counting the breaths/minute and recorded every 5 minutes. Intra-anaesthetically monitored data were recorded every 5 minutes.

The skin area of the scrotum was clipped and disinfected and cats underwent standard orchiectomy. An incision was performed over the scrotum and the tunica vaginalis. The testicles were exposed and their spermatic cord with its vessels was ligated with an absorbable suture. Surgery time from the first skin incision to the end of surgical procedures was recorded. At the end of the surgery, the effects of medetomidine were antagonised by administering 0.15 mg/kg of atipamezole (Antisedan, Orion Corporation, Espoo, Finland) intramuscularly. The administration of atipamezole was recorded as time-point zero.

4.4. Postanaesthetic evaluation of sedation, behavioural reactions, analgesia and physiological parameters

After medetomidine antagonisation with atipamezole, the cats were placed into the pediatric incubator (25°C) and were video recorded for one hour. Behavioural reactions to provoked stimuli, analgesia and physiological parameters were evaluated directly by the anaesthesist while specific reactions to the treatment drugs, sedation, environmental interaction, body position at rest and the overall objective evaluation were evaluated by another veterinarian. Both observers were unaware of treatment identity.

4.4.1. Physiological data

Heart rate (HR), respiratory rate (RR), pulse rhythm and rectal temperature were obtained 30 and 60 minutes after atipamezole administration and the HR and RR difference to baseline values were also calculated at these time-points.

4.4.2. Analgesia

Analgesia was evaluated at 30 and 60 minutes after atipamezole administration by means of a visual analogue scale (VAS; 0mm = no evident signs of pain, 100mm = worst possible pain). If cats showed VAS ≥ 15mm, butorphanol
0.2 mg/kg was provided intramuscularly as rescue analgesic.

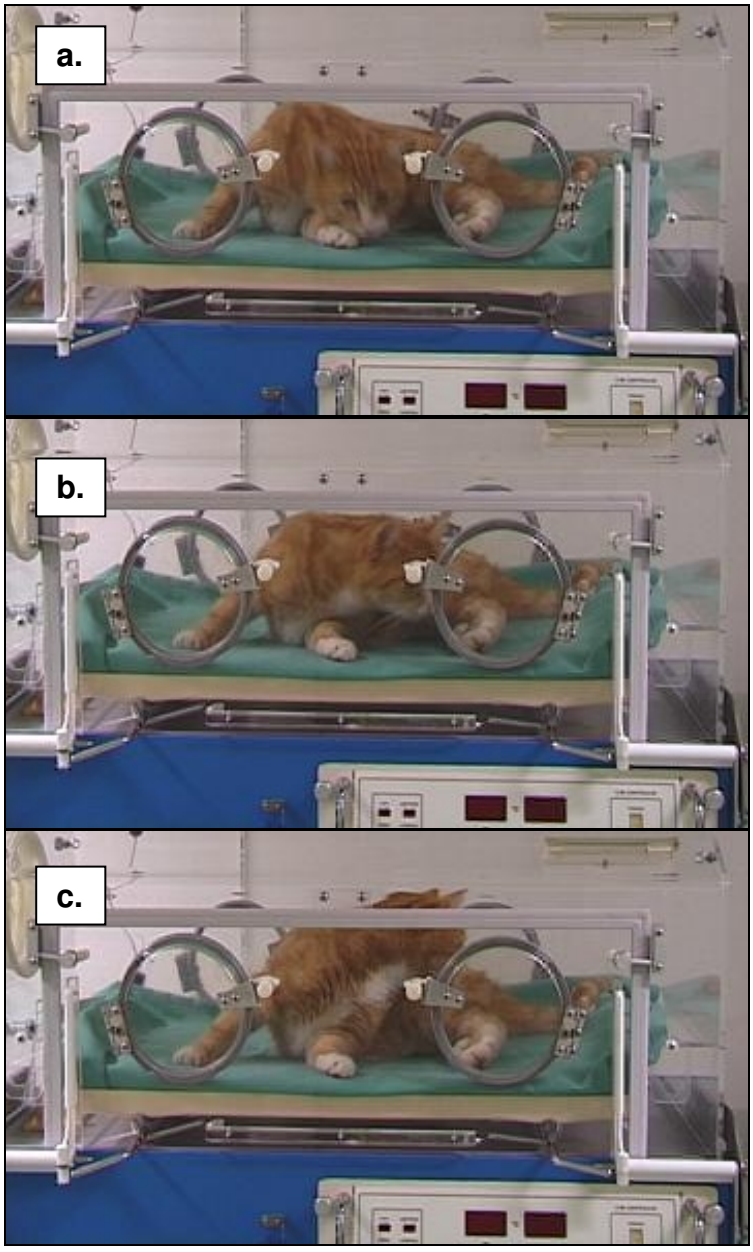
4.4.3. Behavioural responses

4.4.3.1. Unprovoked behaviour

The overall behavioural effects of the tested drugs in the undisturbed subjects were evaluated at 30 and 60 minutes after atipamezole administration using the following scoring system:

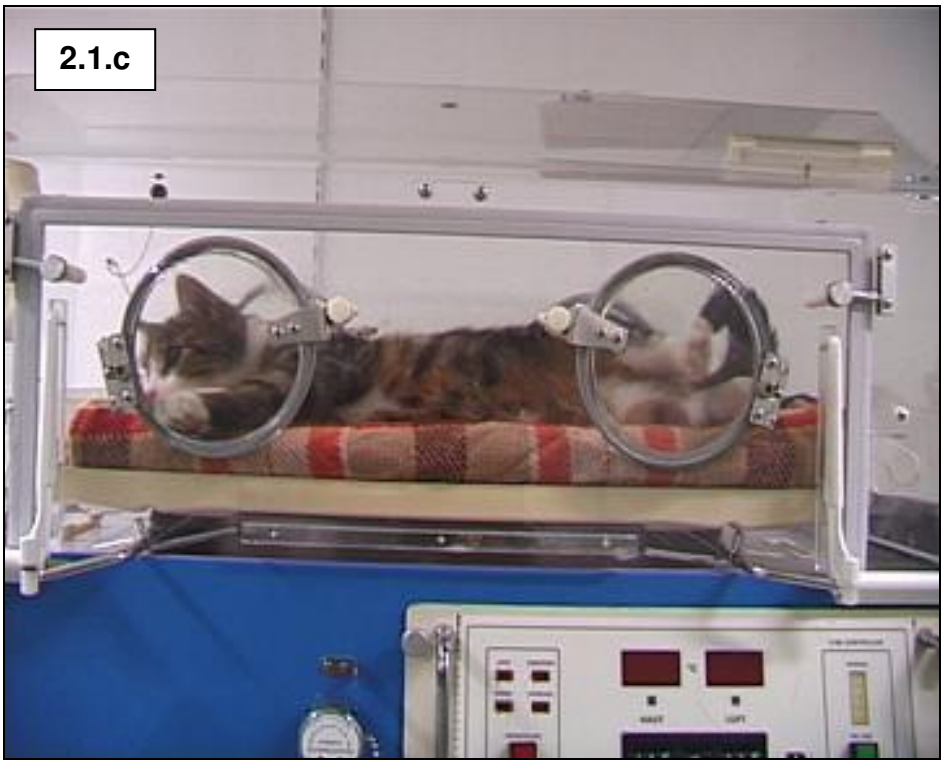
0 = Normal behaviour pattern (quiet, grooming, attentive)
1 = Minor changes (turns head, salivation, minor ataxia, minor excitation)
2 = Moderate changes (restless moaning, moderate ataxia, moderate excitation)
3 = Severe changes (unsolicited vocalisations, very restless, expiratory grunts, rolling over, climbing the cage, severe ataxia, severe excitation)

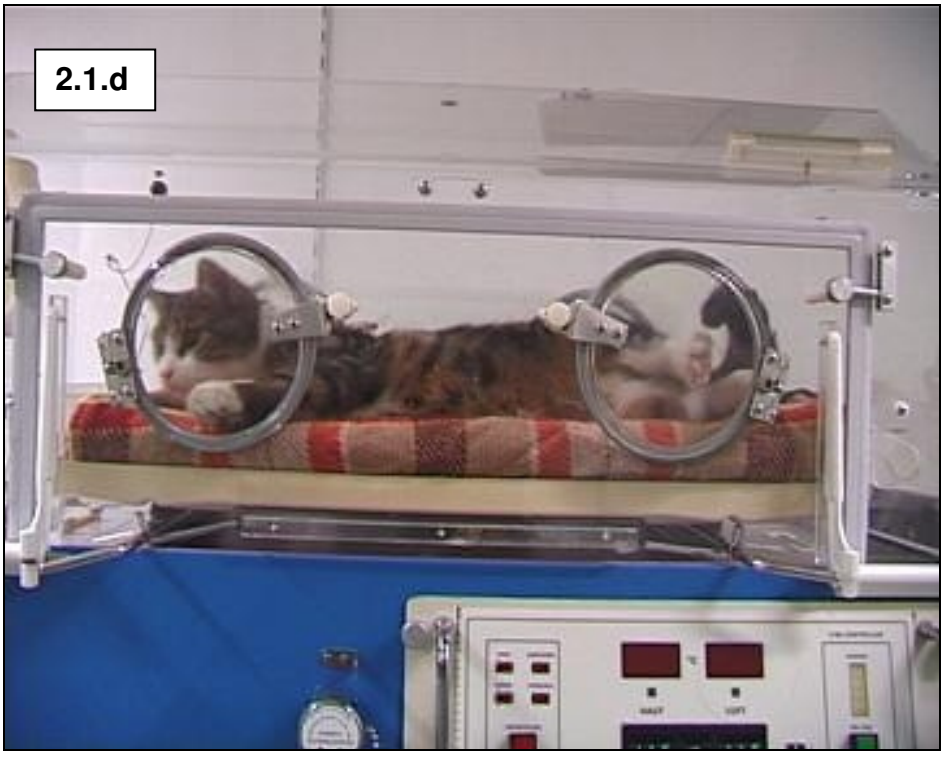
Picture 1: Normal behaviour (quiet)



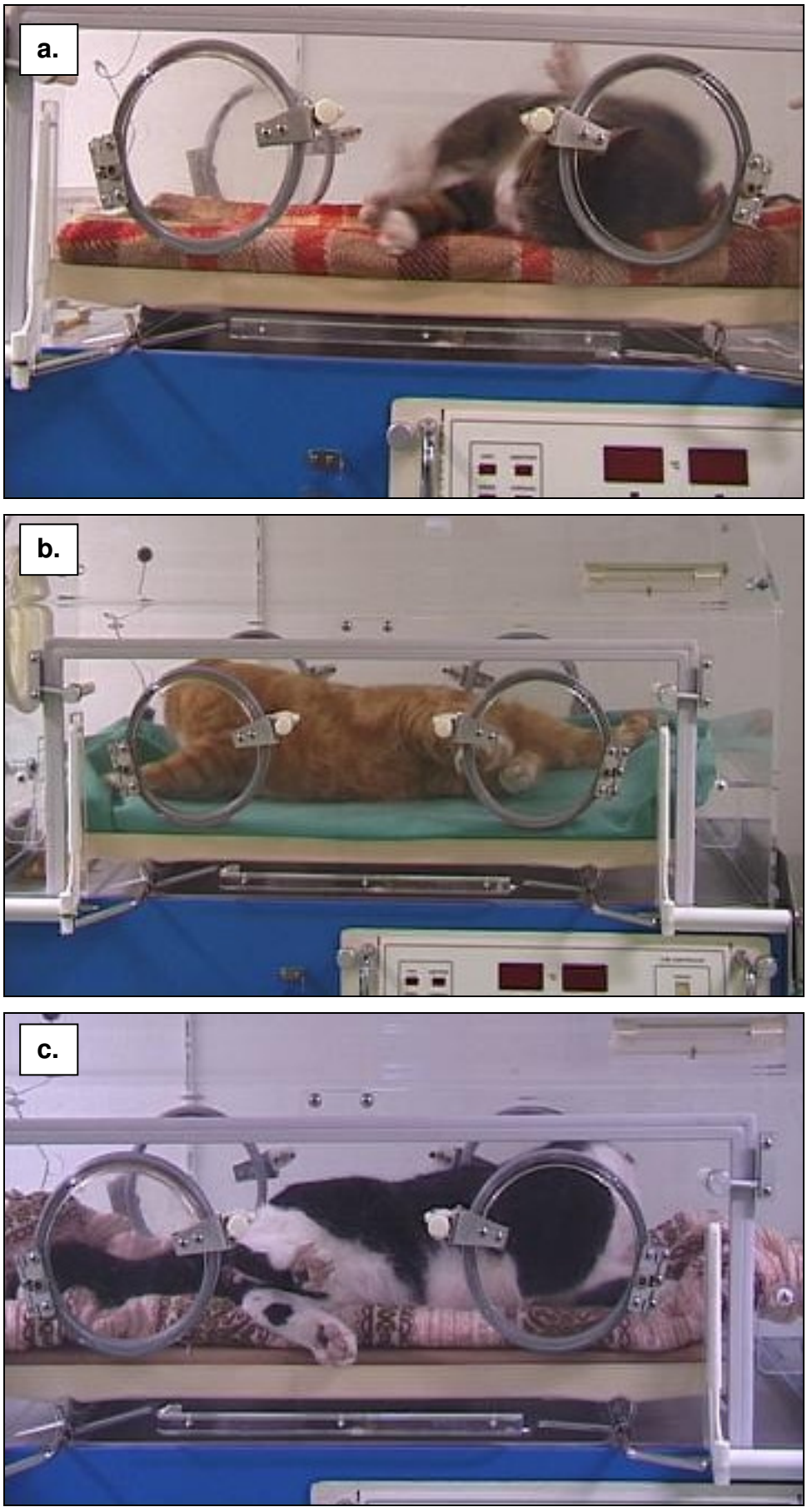
Picture 1.1.a-c: Normal behaviour (attentive)

Picture 2.1.a-b: Minor changes (turns head)

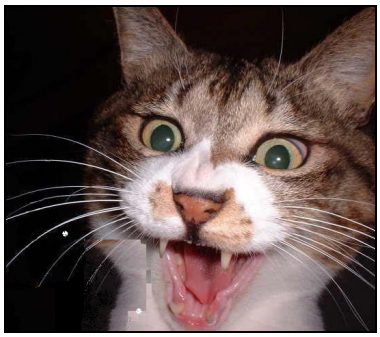




Picture 2.1.c-d: Minor changes (turns head)



Picture 3.a-c: Moderate changes (moderate ataxia)



Picture 4: Severe changes (unsolicited vocalisations)

4.4.3.2. Behavioural responses to external stimuli (Provoked behaviour)

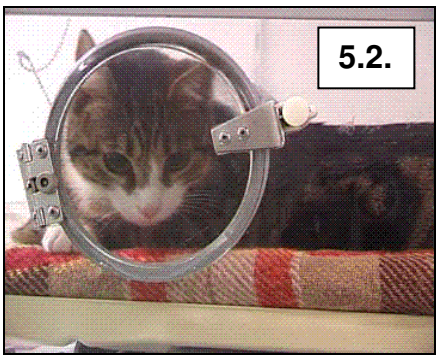
Behavioural responses to external stimuli were obtained and scored by interacting with the patients at 30 and 60 minutes after atipamezole administration as follows:

0 = Normal behavioural responses (normal for the expected conditions)
1 = Minor exaggeration of responses (sensitive to light, sensitive to noise)
2 = Moderate exaggeration of responses (hypersensitive to light and/or to noise, moderate excitation)
3 = Violent exaggeration of responses (aggression, intend to escape, severe excitation)

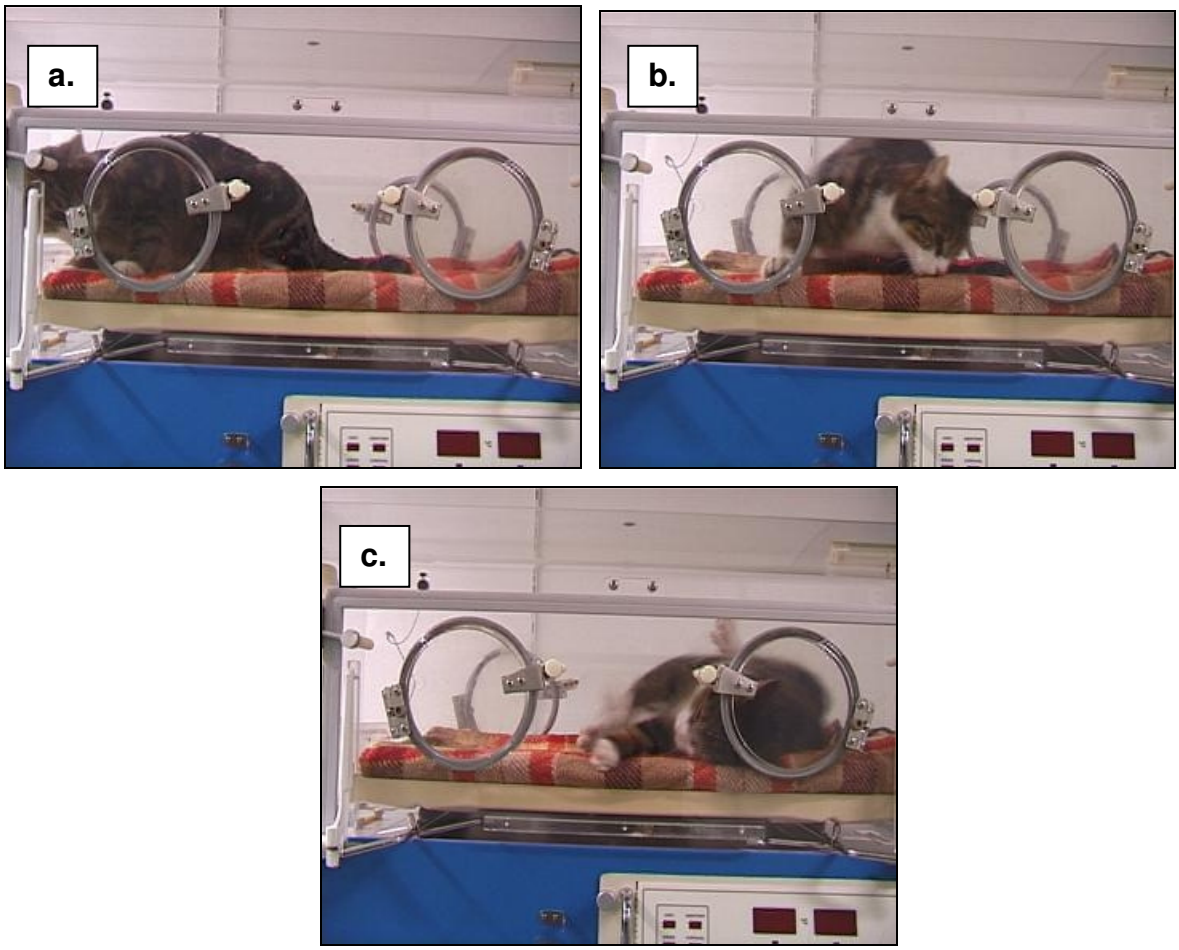
4.4.3.3. Specific behavioural reactions to test drugs

The presence (1=yes) or absence (0=no) of specific behavioural reactions to racemic and S-ketamine anaesthesia that were identified in a previous study (Eichenberger 2005) like mydriasis, tongue movements, “disorientation”, falling towards one side and “licking the lips” frequently were evaluated during two 30 minutes period intervals and recorded.

Picture 5.1: Mydriasis



Picture 5.2: Mydriasis



Picture 6.a-c: “Disorientation” and falling towards one side.

Picture 7: Frequent tongue movements and “licking the lips”.

Muscle tone

Muscular tone was evaluated at 30 and 60 minutes post medetomidine antagonisation and scored as:

1 = increased (stiffness)

0 = normal

- 1 = decreased (relaxed)

Picture 8.1: Increased muscular tone (stif hindlegs)

Picture 8.2: Increased muscular tone (stif hindlegs)

Picture 9: Normal muscular tone

Picture 10: Relaxed muscular tone

4.4.4. Body position and sedation

In order to evaluate the patient's ability to regain the normal motoric function the degree of sedation and the position of their bodies were scored and recorded every 5 minutes after atipamezole administration as follows:

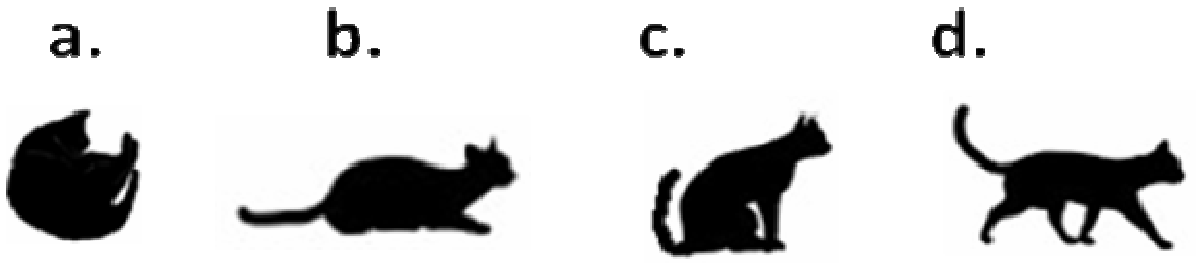
Body position:

0 = lateral recumbency

1 = sternal recumbency

2 = sitting

3 = standing



Picture 11.a-d: a: lateral recumbency, b: sternal recumbency, c: sitting, d: standing

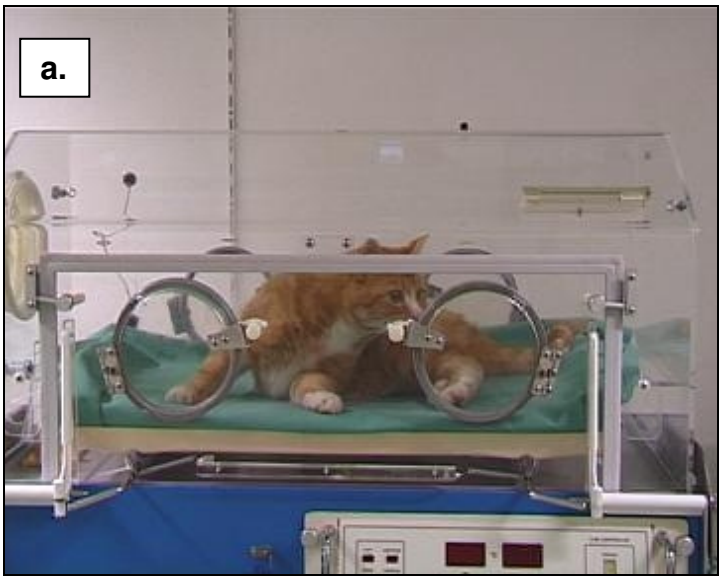
Sedation:

0 = no sedation (fully alert)

1 = poor sedation (alert but with somnolence)

2 = moderate sedation (drowsy, but occasionally restless)

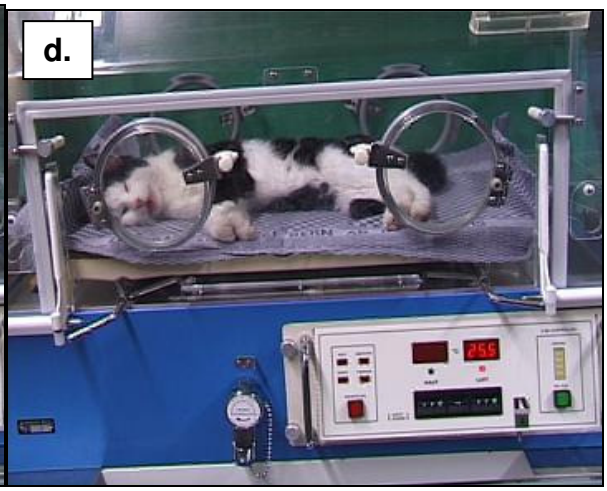
3 = deep sedation (sleeping comfortable)



Picture 12.a: No sedation

Picture 12.b: Poor sedation

Picture 12.c: Moderate sedation



Picture 12.d: Deep sedation

4.5. Recovery times and general follow-up

Time to regain the sternal and the standing position after atipamezole administration (time-point zero) was obtained and recorded. Sixty minutes after time-point zero the experience was concluded and the antibiotic cefazoline (Kefzol, Teva Pharma AG, Aesch, Switzerland) at a dose of 20 mg/kg and the long term analgesic carprofen (Rimadyl, Pfizer, New York, USA) at a dose of 4mg/kg were administered subcutaneously. The cats were returned to their owners the same day of the surgery.

4.6. Statistical methods

The NCSS 2004 (Kaysville, Utah, USA) software package was used to perform the statistical evaluation. All data were analysed for normal distribution with the Shapiro-Wilk W test.

The statistical significance of the difference between groups for parametric data was assessed with Student's t-tests or Analysis of Variance tests and for non parametric variables by using Mann-Whitney U tests or Kruskal-Wallis One-Way ANOVA on Ranks tests. For comparisons with baseline values the data was paired using every cat as its own match. Chi-square tests for independence in a contingency table were used to compare proportions and if there was any association between two classification variables.

For all tests, overall $P<0.05$ was considered the minimum level of statistical significance. A trend towards a statistical significance was defined as $P<0.1$. Parametric data are presented as mean ± standard deviation and non-parametric data are presented as median and range or interquantile range (box-plots), or displayed as scatter-plots. Proportions are presented as percents.

5. RESULTS

5.1. Test animals and pre-examination clinical data

A total of 20 male non-castrated cats were presented to the study and were included (group A: S-Ket: n=10; group B: RacKet: n=10). No statistically significant differences between groups were detected regarding the age (1 ± 0.6 years for both groups; P = 0.98) and weight (S-Ket: 3.4 ± 0.5kg; RacKet: 3.5 ± 0.5kg; P = 0.72) of the cats. There were no statistically significant differences in heart rate (HR) values (group A: 167 ± 29 beats/minute; group B: 157 ± 20 beats/minute; P = 0.38) or in respiratory rate (RR) values between groups, although there was a trend (P = 0.08) for lower RR values in group A (43 ± 12 breaths/minute) compared with group B (53 ± 12 breaths/minute). All cats were considered to be healthy on the basis of clinical examination and suitable to receive anaesthesia. All cats in group A and seven cats in group B were ranked as ASA I and three cats in the group B were ranked as ASA II.

5.2. Surgery and anaesthesia

All anaesthetic and surgical episodes were uneventful. Postoperative rectal temperature remained above 37.5°C for cats in both groups. There were no signs of intra-operative bradycardia, arrhythmias, apnoea, or hypoxemia. All cats achieved an acceptable anaesthetic depth for the surgical procedures and had a complete recovery from anaesthesia. Mean surgery time was 6.6 ± 2.5 minutes for S-Ket and 7.8 ± 2.7 minutes for RacKet (P = 0.32).

5.3. Post-operative heart rate and respiratory rate differences, pulse rhythm and rectal temperature

Although there were no significant differences for heart rate (HR) values between groups (P = 0.4) 30 min after medetomidine antagonisation, both groups showed higher HRs compared with baseline recordings (S-Ket: HR = 215 ± 39 beats/minute, P = 0.003; RacKet: HR = 202 ± 23 beats/minute, P = 0.008). No significant differences were recorded for HR at 60 minutes between groups (P = 0.11) and for S-Ket (HR = 184 ± 21 beats/minute) compared with baseline (P = 0.13), although at that time point HR values were significantly higher for RacKet (HR = 202 ± 23 beats/minute, P = 0.001) compared with baseline. No arrhythmias were detected.

For S-Ket, values of respiratory rates (RR) at 30 minutes (62 ± 10 breaths/minute) and at 60 minutes (63 ± 17 breaths/minute) were statistically higher compared with baseline values (P = 0.004 and P = 0.002, respectively). No differences were detected for RRs in RacKet group at 30 minutes (53 ± 17 breaths/minute, P = 0.97) or at 60 minutes (53 ± 11 breaths/minute, P = 0.94). However, differences between groups in regards to RR values were not significant at 30 minutes (P = 0.16) nor at 60 minutes (P = 0.17).

All cats had rectal temperature values above 38℃ at any evaluated time point during the anaesthesia recovery phase.

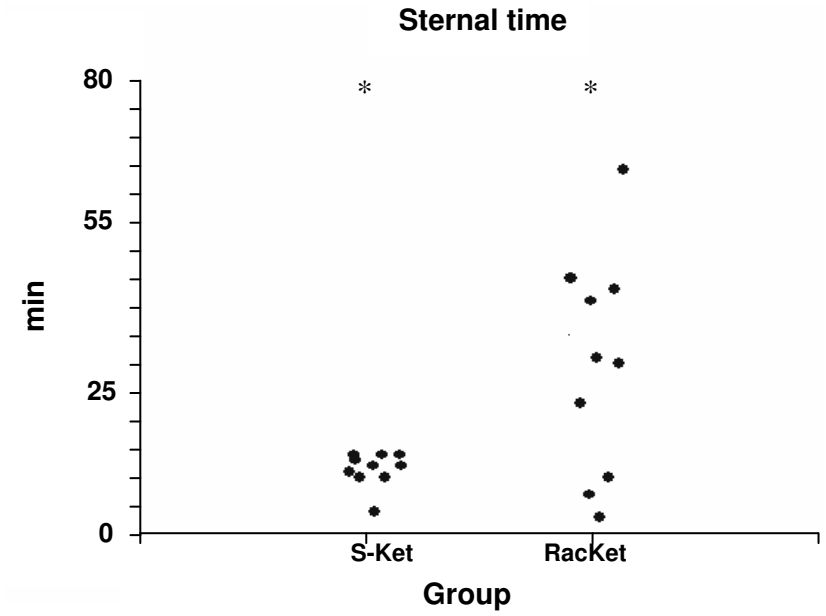
5.4. Time to sternal and standing positions

Cats allocated to S-Ket reached the sternal recumbency significantly (P = 0.008) faster (11.4 ± 3 minutes) compared with those allocated to RacKet (29.7 ± 19.3 minutes; Fig 14 a). Subsequently, the cats in group A stood up significantly (P = 0.005) faster (22.1 ± 6.1 minutes) than cats in group B (44.3 ± 21.5 minutes; Fig. 14 b).

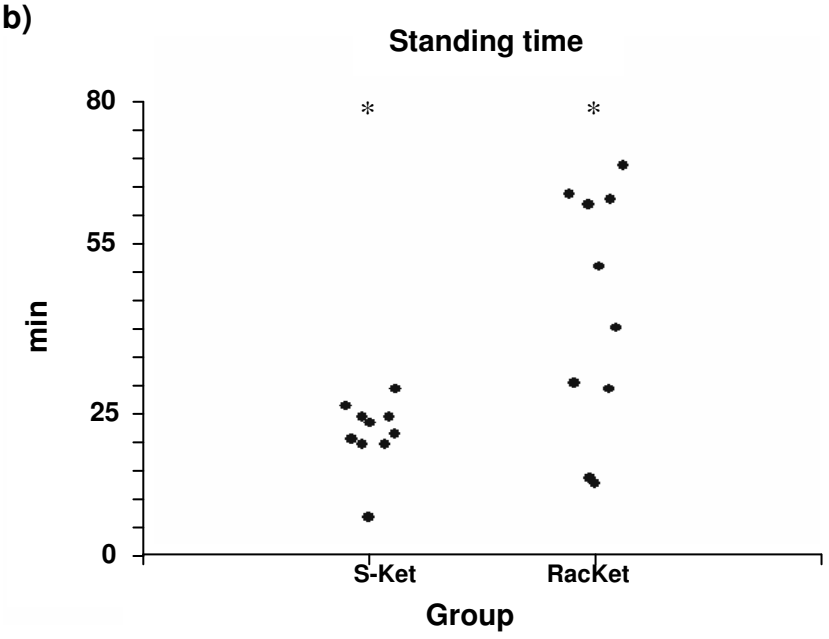
Figure 14: Time to sternal and standing positions

*P<0.05 for statistical comparisons between groups

a)



b)



5.5. Analgesia

VAS values were low for all cats at any evaluated time point (S-Ket: 30 min = 5.1 ± 2.1mm, 60 min = 4.3 ± 1.8mm; RacKet: 30 min = 5.1 ± 3.4mm, 60 min = 4.3 ± 2.6mm). No cat required administration of butorphanol during the one hour examination period.

5.6. Behavioural reactions

All cats had normal behaviour patterns (score = 0) before anaesthesia but one cat in S-Ket, which showed a behavioural response to external stimuli score of 3 before drug administration because it intended to escape. None of the cats presented to this study were aggressive before drug administration.

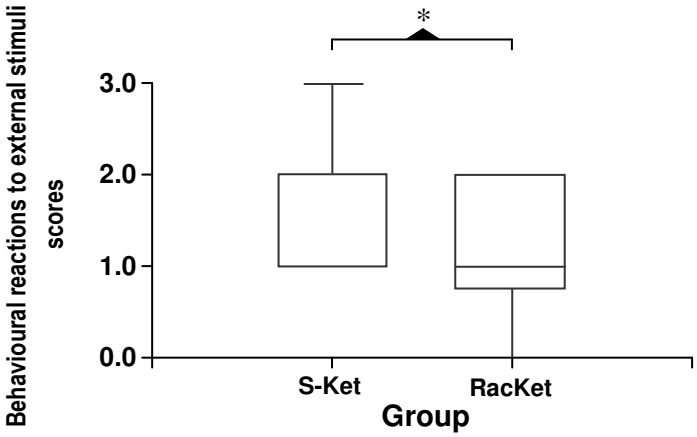
Unprovoked behaviour scores were similar (P = 1) for both groups at 30 minutes (1, range 1-2). Although no significant differences were found between groups at 60 minutes, there was a trend (P = 0.09) for lower scores for S-Ket (1, range 0-1) compared with RacKet (1, range 0-2).

The scores representing the external stimuli (Fig. 15: a and b) were significantly higher (P = 0.04) in cats allocated to S-Ket at 30 minutes compared with RacKet, while differences between groups found 60 minutes after time-zero were not significant (P = 0.43).

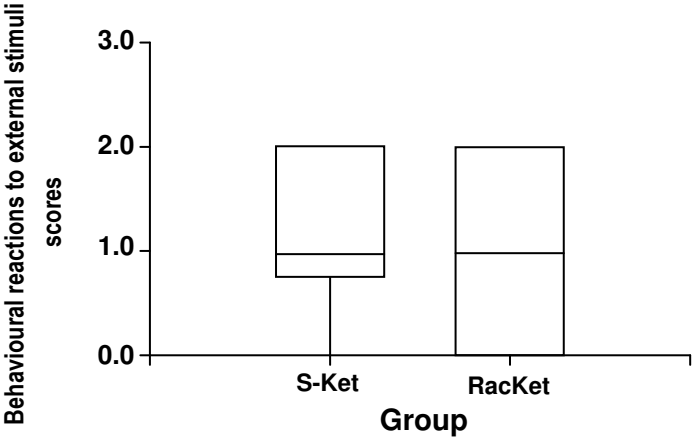
Figure 15: Behavioural reactions to external stimuli

*P<0.05 for statistical comparisons between groups

a) at 30 minutes



b) at 60 minutes



All cats (1 = 100 %, 0 = 0% for both groups) presented mydriasis at 30 minutes (P = 1), and all but one cat in RacKet (S-Ket: 1= 100%, 0 = 0%; RacKet: 1 = 90%, 0 = 10%) at 60 minute after time-point zero (P = 0.3). Both groups showed similar extents (P = 0.65) of “disorientation”/falling towards one side (S-Ket: 1 = 60%, 0 = 40%; RacKet: 1 = 50%, 0 = 50%) and although more cats in S-Ket showed more tongue movements/”licking the lips” events (1 = 70%, 0 = 30%) than those in RacKet (1 = 40%, 0 = 60%) these differences were not statistically significant (P = 0.17).

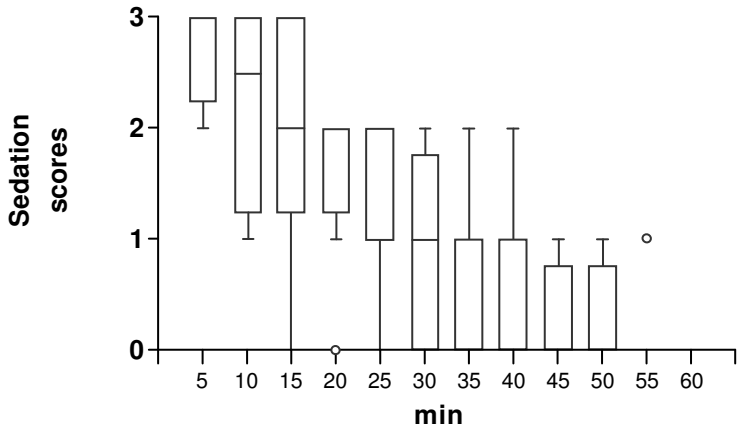
No significant (P = 0.5) differences between groups were found at 30 minutes (S-Ket: 1 = 70%, 0 = 30%, -1 = 0%; RacKet 1 = 70%, 0 = 20%, -1 = 10%) for scoring of the muscular tone. Similarly, no significant (P = 0.5) differences between groups were found at 60 minutes (S-Ket: 1 = 20%, 0 = 80%, -1 = 0%; RacKet 1 = 30%, 0 = 70%, -1 = 0%) when evaluating muscular tone.

Sedation

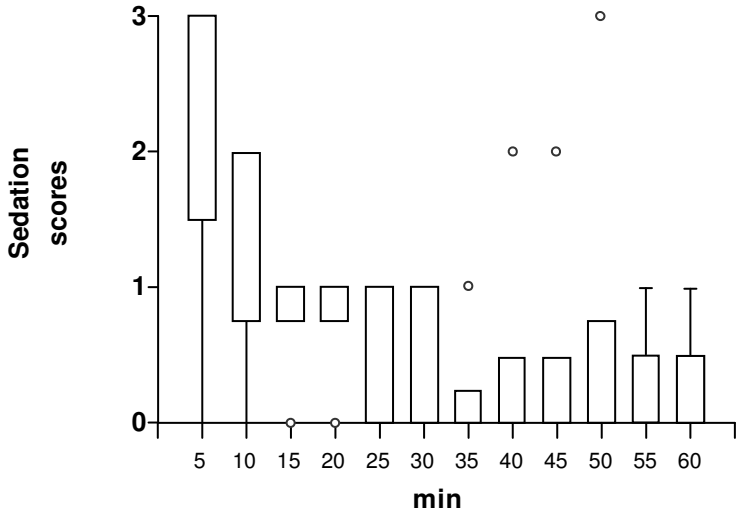
Cats allocated to RacKet had significantly higher (P = 0.04) sedation scores than cats allocated to S-Ket (Fig. 16: a and b).

Figure 16: Sedation scores

a) RacKet



b) S-Ket



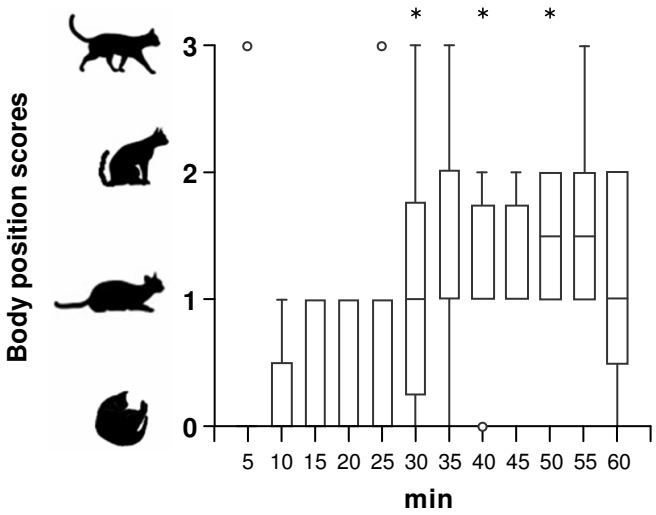
Body position

Body position scores were significantly (P = 0.001) higher for S-Ket compared with RacKet (Fig. 17: a and b). Cats allocated to S-Ket showed more sitting and standing events than cats allocated to RacKet.

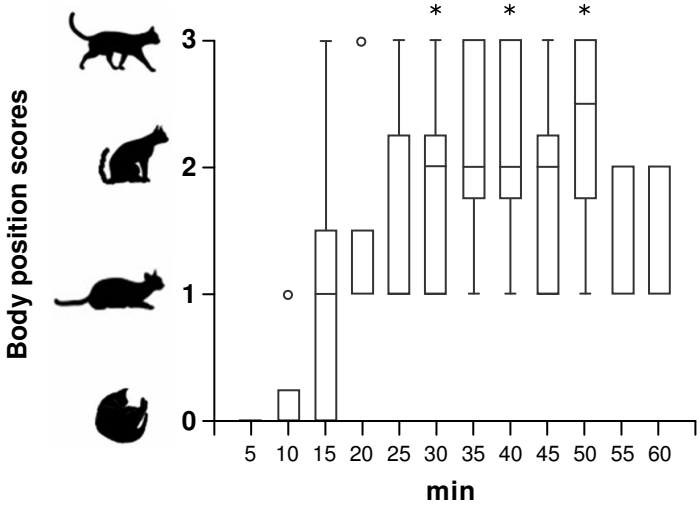
Figure 17: Body position scores

*P<0.05 for statistical comparisons between groups

a) RacKet



b) S-Ket



6. DISCUSSION

Early human studies of ketamine isomers (White et al. 1980) appeared to demonstrate that the S-isomer of ketamine produced less psychic emergence reactions than either the R-isomer or the racemic mixture. Moreover, the S-enantiomer has proven advantageous reaching an identical plane of anaesthesia with half of the racemic dose. S-ketamine administered at half of the racemic ketamine dose was also found to provide a similar degree of analgesia to clinically healthy cats (Stelter 2001) undergoing elective spay. In the current study an equipotent dose of racemic ketamine (10 mg/kg) and S-ketamine (6 mg/kg) was chosen. This equipotency was obtained from a previous study in which the required doses of either compound necessary for producing similar anaesthetic conditions to place an orotracheal tube in cats were acquired (Wiederstein and Auer 2003). Similar doses have been also used in moderate anaesthetic-risk (ASA III) feline patients in which S-ketamine provided a significantly faster recovery period and better post-operative analgesia and emergence quality than the racemic mixture (Baumgartner et al. 2002). Contrarily, similar recovery quality and immediate post-surgical analgesia were observed in a previous study in female cats undergoing routine ovariectomy which received similar anaesthesia induction doses of racemic and S-ketamine than the present study (Larenza et al. 2004). However, in the latter anaesthesia was maintained with isoflurane in oxygen. The authors could not demonstrate any differences between groups in regards to behavioural reactions and analgesia during the recovery phase of anaesthesia and concluded that it remained unclear whether these results were related to the similar anaesthetic actions of the two compounds or if potentially dissimilar results were masked by the inhaled agent isoflurane and/or by gender-specific drug effects. Interestingly, S-ketamine elimination was similar after single enantiomer administration or within the racemate in ponies anesthetised with isoflurane at one minimal alveolar concentration (MAC), but S-ketamine elimination was favoured when given alone, if the ponies were sedated with the alpha-2 adrenoceptor agonist xylazine (Larenza et al. 2007a; Larenza et al. 2007b). These results suggested that the coadministered drug might have a significant impact over the overall metabolism of ketamine enantiomers.

Based on these studies, it was postulated that the association of S-ketamine with an alpha-2 adrenoceptor agonist would have a positive effect over this enantiomer elimination, that might be translated as faster recoveries from anaesthesia in cats. In the present study, in which both groups received medetomidine as a sedative agent, the cats that received S-ketamine had a faster recovery compared with those receiving racemic ketamine, supporting the theory that enantiomeric metabolism might be favoured/preserved in the presence of an alpha 2-agonist.
In the present study sedation scores were assessed on the basis of a numerical scoring system. After surgery all twenty cats were sleeping comfortable. Antagonisation of medetomidine by means of antipamezole immediately after surgery caused continuous decrease of sedation scores. At the end of observation (60 minutes after extubation) most cats were fully awake. Transition time from middle to more slightly sedation was significantly different between the two groups. Cats allocated to racemic ketamine had significantly higher sedation scores than cats allocated to S-ketamine. Cats with S-ketamine showed faster postoperative recovery than cats with racemic ketamine, since the dosage of S-ketamine (6 mg/kg) was lower than of the racemate (10 mg/kg). This lower dose of S-ketamine has the important advantage that the substance load for the patient is lower. Other studies came to similar conclusions (Baumgartner et al. 2002; Larenza et al. 2004; Stelter 2001). Clinical and electroencephalographic (EEG) effects of S-ketamine and racemic ketamine were compared in a human medical study. Sedation period and awakening phase were significantly shorter for patients with S-ketamine (White et al. 1980).
The behavioural changes after racemic ketamine administration are well known and have been the reason for the reluctance of many practitioners to administer such a drug to their patients (Kohrs and Durieux 1998). In humans, hallucinatory behaviour, which may progress to delirium, may occur during emergence from racemic ketamine anaesthesia. These effects occur because of inhibition of the inferior cunniculus and medial nucleus geniculatum, which in turn leads to misinterpretation of auditory and visual stimuli (White et al. 1982). In cats recovering from ketamine anaesthesia the following emergence reactions were observed: ataxia, increased motor activity, hyperreflexia, touch sensitivity, hallucinations, which can enhance up to delirium and aggressiveness (Beck 1976; Velisek and Mares 1990; White et al. 1982).

In this study, a modified version of a table designed to evaluate specific post-ketamine reactions was used (Eichenberger 2005; Larenza et al. 2004).
In studies peformed in human beings it could be observed that dream experiences arose in similar frequency, but in different quality after S-ketamine administration comparison with racemic ketamine (Dundee and Wyant 1988; White et al. 1980). Excitations and disorientation after S-ketamine administration were rarer than after the racemate (White et al. 1980). In this study, both groups showed minor to moderate behavioural changes, although, when undisturbed, cats in the S-Ket group showed more often normal behavioural events towards the end of the examination period. However, cats in the S-Ket group had a trend for stronger reactions when the observer interacted with them at 30 min. Cats in RacKet group probably reacted in a more calm fashion at that time point because they were more sedate.
During emergence from anaesthesia all twenty cats showed head movements. A typical behaviour characteristic, which was seen in all cats, was moving the head from one side to the other. This behaviour pattern might occur because of disorientation during emergence from anaesthesia and was not group specifically recognisable. This result correlates with the statement of the observer that all cats exhibited disorientation. Disorientation is not only caused by dissociative anaesthetics, but can also be observed after administration of other anaesthetics. Further behavioural characteristics, which occur due to disorientation, are switching weight from one leg to the other, falling to one side and rolling over. Also these characteristics were observed in cats, which were classified as moderate behavioural changes. Ketamine causes increased salivation (Hall et al. 2001). In the present study all twenty cats showed tongue movements which could be related to increased saliva production.
Significant activity of racemate at the κ-opioid receptors, which are probably responsible for the psychomimetic side effects, is a possible explanation. S(+)-ketamine showed less behavioural alterations than R(-)-ketamine in human patients. As S(+)-ketamine interacts more with μ- than κ-opioid receptors, the behavioural changes might be reduced when using this enantiomer instead (Kohrs and Durieux 1998; Kress 1997).
An influence of other components of the anaesthesia protocol over the behavioural characteristics cannot be excluded.

As medetomidine sedative effects were reversed with atipamezole after surgery in all cats the probability of its influence over the observed behavioural changes should be minimal. However, the alpha-2 antagonist atipamezole has been reported to induce some behavioural changes in cats. However, since both groups received similar doses of atipamezole, the differences observed between groups should not be related to this compound.

Evaluation of pain in animals is difficult since they cannot verbally communicate. Different methods for evaluating pain in animals were tested in past years, but until today no validated standard methods exist for cats. Further studies in the future are needed in order to attain more comprehensive knowledge. Most of the current methods to evaluate pain in animals are complex and are based on subjective observations or use of multifactorial parameters, thus less pain specific. The use of vital parameters to estimate pain (for example; heart rate and respiratory rate) can lead to erroneous interpretation because they might be altered not only by nociceptive stimuli but also by the drugs themselves and by the environmental influence. Specific behavioural reactions can be used as well to assess the degree of pain. Unfortunately, as ketamine itself promotes behavioural changes, methods to assess pain containing behavioural parameters were excluded in the present study. Instead, immediate postoperative pain was evaluated by using a VAS, a common and simple system very popular to quantify pain in pediatric patients. In order to minimise the impact of the subjective component of this method, the same observer assessed all patients. In this case, both groups showed very low VAS values and no cat required butorphanol suggesting that racemic ketamine and S-ketamine provided very good postoperative analgesia. However, it must be taken into consideration that cats in S-Ket group were given only 60% of the racemic dose. These results might infer that S-ketamine exhibits a stronger analgesic effect than racemic mixture. This is in agreement with a previous study in cats with increased anaesthetic risk receiving racemic ketamine or S-ketamine (Baumgartner et al. 2002).

The mechanism of action of ketamine enantiomers as analgesics is complex and not fully understood. Ketamine selectively depresses neuronal function in parts of cortex and thalamus, while simultaneously stimulates parts of the limbic system, including hippocampus (Miyasaka and Domino 1968; Massopust et al. 1972).

Nociceptive cells of the reticular formation are inhibited and laminae I und V in the feline dorsal spinal horn are activated. Most of these actions over the CNS as well as those responsible for analgesia come from the competitive inhibition that ketamine exerts over the NMDA receptor. Interestingly, S(+)-ketamine showed 4 times higher affinity for the NMDA receptor than R(-)-ketamine did, suggesting that the stronger analgesic effect of this enantiomer is a result of its higher affinity for the mentioned receptor. In addition S(+)-ketamine showed a stronger interaction with opioid receptors compared with R(-)-ketamine. However, the analgesic effects of ketamine that are a result of its interaction with opioid receptors are not the most relevant ones. Ketamine often produces significant increases in blood pressure and heart rate (HR) and increases in pulmonary artery pressure have been reported. These effects are due to sympathetic stimulation; ketamine's direct effect on the heart is depressant, S(+)-ketamine less than R(-)-ketamine (Kohrs and Durieux 1998). Although there were no significant differences for HR values between the two groups 30 min after medetomidine antagonisation, both groups showed higher HRs compared with baseline recording. No significant differences were recorded for HR at 60 minutes between groups and for S-Ket compared with baseline, although at that time point HR values were significantly higher for RacKet compared with baseline. Contrarily, other studies showed contradictory results (Baumgartner et al. 2002; Larenza et al. 2004). Female cats undergoing spay surgery anesthetised with similar doses of RacKet and S-Ket to this study and Isoflurane in oxygen showed lower HRs after RacKet compared to S-Ket. On the other hand, cats with increased anaesthetic risk evidenced lower HRs after S-Ket compared with Racket administration. The authors postulated that these results suggested a better analgesia for cats allocated to S-Ket compared with RacKet. However, when comparing these it should be considered that anaesthesia protocols were not identical. In the present study medetomidine at a dose of 30 µg/kg was administered intramuscularly for pre-anaesthetic sedation unlike the above mentioned studies in which midazolam or isoflurane were also co-administered. In addition, the different surgery times and postoperative recovery times could have influenced the HR as well.

Ketamine effects on the respiratory system are generally beneficial: it is a well documented bronchodilator, it causes minimal respiratory depression with only mild hypercapnia in clinically relevant doses, and protective airway reflexes are more likely to be preserved than with other IV anaesthetics (Kohrs and Durieux 1998).

However, increased oral secretions can occur. In this study, for S-Ket, values of respiratory rate (RR) at 30 minutes and at 60 minutes were statistically significant different compared with baseline values. The reasons for these differences remain unclear. The intrinsic effects of S-ketamine on the respiratory center are poorly understood and research studies evaluating the effects of ketamine enatiomers on the respiratory system are inconclusive (Larenza et al. 2007a; Sarton et al. 2001). In addition, some factors such as pain and hyperthermia may produce tachypnea (Kafer and Marsh 1977). In this case, cats allocated to S-Ket were adjudged to have low VAS values and postanaesthetic rectal temperature measurements were within normal ranges. However, several other factors not evaluated in this study such as anxiety, arterial partial pressure of carbon-dioxide and oxygen among others may also increase the postoperative respiratory rate (Kafer and Marsh 1977). No differences were detected for RRs in RacKet group at 30 minutes or at 60 minutes. However, differences between groups in regards to RR values were not significant at 30 minutes or at 60 minutes.

7. CONCLUSION

Anaesthesia with S-ketamine, at 60% of racemic ketamine, provided faster recoveries and increased postoperative respiratory rates. Cats allocated to RacKet had increased heart rates postoperatively at 30 and 60 minutes, while those allocated to S-Ket had increased heart rates only at 30 minutes. At 60 minutes, undisturbed cats in S-Ket showed a trend towards fewer behavioural changes. Cats in RacKet were more sedate at 30 minutes and responded with a lower intensity to external stimulation. Immediate postoperative analgesia was judged adequate for both drugs.

In conclusion, it can be postulated that the results of the study point to the fact that S-ketamine given to the cat in a dosage of 60% of racemic ketamine serves as an adequate anaesthetic and thus the patient can be anaesthetised with a smaller substance load. Emergence from anaesthesia with ketamine solutions tested in this study produced similar behavioural reactions. However, cats treated with S-ketamine showed less lasting episodes of abnormal behaviour reactions and sedation, and overall shorter postoperative recovery periods than racemic ketamine.

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CURRICULUM VITAE

Name	Camila Nicole Balmer
Geburtsdatum	25. September 1978
Geburtsort	Bern
Nationalität	Schweizerin
Heimatort	Wilderswil BE

1985 - 1989	Primarschule Fraubrunnen
1989 - 1994	Sekundarschule Fraubrunnen
1994 – 1998	Gymnasium Burgdorf
Juni 1998	Maturität Typus D
1998 - 2000	Biologiestudium an der Universität Bern
Juni 2000	Erstes Vordiplom in Biologie
2000 - 2007	Studium der Veterinärmedizin an der Universität Bern
September 2007	Staatsexamen der Veterinärmedizin an der Universität Bern